

University of Groningen

The 2-aminotetralin system as a structural base for new dopamine- and melatonin-receptor agents

Copinga, Swier

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

1994

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Copinga, S. (1994). *The 2-aminotetralin system as a structural base for new dopamine- and melatonin-receptor agents*. s.n.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

**THE 2-AMINOTETRALIN SYSTEM AS
A STRUCTURAL BASE FOR NEW
DOPAMINE- AND MELATONIN-RECEPTOR AGENTS**

RIJKSUNIVERSITEIT GRONINGEN

**THE 2-AMINOTETRALIN SYSTEM AS
A STRUCTURAL BASE FOR NEW
DOPAMINE- AND MELATONIN-RECEPTOR AGENTS**

PROEFSCHRIFT

ter verkrijging van het doctoraat in de
Wiskunde en Natuurwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus Dr. F. van der Woude
in het openbaar te verdedigen op
vrijdag 21 oktober 1994
des namiddags te 4.00 uur

door

Swier Coppinga

geboren op 24 januari 1965
te Groningen

Promotor

Prof. Dr. H.V. Wikström

Co-Promotor

Dr. C.J. Grol

voor mijn ouders

Promotiecommissie

Prof. Dr. U. Hacksell
Prof. Dr. R.M. Kellogg
Prof. Dr. J. Zaagsma

Paranimfen

Fokje Coppinga
Evert Homan

The studies described in the second part of this thesis were financially supported by Glaxo Group Research Ltd. (Ware, Hertfordshire, UK).

Cover

Cor and Eric Grol - The "genesis" of the molecular structures of 5,6-dihydroxy-2-[N-*n*-propyl-N-2-(2-thienyl)-ethylamino]tetralin [5,6-(OH)₂-PTAT] and 8-methoxy-2-(acetamido)tetralin [8-MeO-AAT].

Printing

Krips Repro, Meppel, The Netherlands

*It is but sorrow
to be wise
when wisdom profits not*

Sophocles (496 BC - 405 BC)
Oedipus the King

TABLE OF CONTENTS

PREFACE	page 1
SCOPE OF THE THESIS	2
 PART I 5,6-(OH)₂-PTAT: A MIXED D₁/D₂-RECEPTOR AGONIST	
 CHAPTER 1 INTRODUCTION PART I	
1.1 DOPAMINE: A NEUROTRANSMITTER IN THE CNS	5
1.2 DOPAMINE RECEPTORS	10
1.3 DOPAMINE-RECEPTOR AGENTS	24
1.4 D ₁ /D ₂ -RECEPTOR INTERACTIONS	36
1.5 REFERENCES	48
 CHAPTER 2 SYNTHESIS OF 5,6-(OH)₂-PTAT: A POTENTIAL MIXED D₁/D₂-RECEPTOR AGONIST	
2.1 INTRODUCTION	65
2.2 5,6-(OH) ₂ -PTAT: A POTENTIAL MIXED D ₁ /D ₂ -RECEPTOR AGONIST	65
2.3 SYNTHESIS OF 5,6-DISUBSTITUTED 2-[N- <i>N</i> -PROPYL-N-2-(2-THIENYL)- ETHYLAMINO]TETRALINS	70
2.4 EXPERIMENTAL SECTION	77
2.5 REFERENCES	84
 CHAPTER 3 PHARMACOLOGICAL EVALUATION OF 5,6-(OH)₂-PTAT: A MIXED D₁/D₂-RECEPTOR AGONIST	
3.1 INTRODUCTION	89
3.2 RESULTS OF PHARMACOLOGICAL EVALUATION	91
3.3 DISCUSSION OF PHARMACOLOGICAL RESULTS	98
3.4 CONCLUSION	100
3.5 EXPERIMENTAL SECTION	101
3.6 REFERENCES	105
 PART II 2-AMIDOTETRALINS: NONINDOLIC MELATONIN-RECEPTOR AGENTS	
 CHAPTER 4 INTRODUCTION PART II	
4.1 MELATONIN: A MAMMALIAN PINEAL AND RETINAL HORMONE	111
4.2 PHYSIOLOGICAL EFFECTS OF MELATONIN	120
4.3 CLINICAL IMPLICATIONS AND PERSPECTIVES OF MELATONIN	122
4.4 MELATONIN RECEPTORS	125
4.5 MELATONIN-RECEPTOR AGENTS	131
4.6 REFERENCES	140

	page
CHAPTER 5 8-METHOXY-2-AMIDOTETRALINS: NONINDOLIC MELATONIN-RECEPTOR AGONISTS	
5.1 INTRODUCTION	149
5.2 8-METHOXY-2-(ACETAMIDO)TETRALIN AND ANALOGUES; POTENTIAL MELATONIN-RECEPTOR AGONISTS	150
5.3 SYNTHESIS OF 8-METHOXY-2-(ACETAMIDO)TETRALIN AND ANALOGUES	152
5.4 PHARMACOLOGICAL EVALUATION OF 8-METHOXY- 2-(ACETAMIDO)TETRALIN AND ANALOGUES	158
5.5 DISCUSSION	162
5.6 CONCLUSION	168
5.7 EXPERIMENTAL SECTION I (CHEMISTRY)	168
5.8 EXPERIMENTAL SECTION II (PHARMACOLOGY)	177
5.9 REFERENCES	179
CHAPTER 6 4-ARYL-2-AMIDOTETRALINS: NONINDOLIC MELATONIN-RECEPTOR ANTAGONISTS AND AGONISTS	
6.1 INTRODUCTION	183
6.2 SYNTHESIS OF 4-ARYL-2-AMIDOTETRALINS	185
6.3 PHARMACOLOGICAL EVALUATION OF 4-ARYL-2-AMIDOTETRALINS	191
6.4 DISCUSSION	192
6.5 EXPERIMENTAL SECTION I (CHEMISTRY)	193
6.6 EXPERIMENTAL SECTION II (PHARMACOLOGY)	203
6.7 REFERENCES	204
GENERAL DISCUSSION	
THE SEMI-RIGID 2-AMINOTETRALIN SYSTEM: A STRUCTURAL BASE FOR ANALOGUES OF BIOLOGICALLY ACTIVE SUBSTANCES	207
REFERENCES	211
SUMMARY	213
SAMENVATTING	216
LIST OF PUBLICATIONS	219
DANKWOORD	221

PREFACE

The research described in this thesis can be divided into two parts as a consequence of the tragic death of Prof. Dr. A.S. Horn on January 2, 1990. The first part belongs to a research project aiming at the development of 2-aminotetralins and related compounds as dopamine-receptor agents. The second part belongs to another research project directed to the development of 2-amidotetralins and related compounds as nonindolic melatonin-receptor agents. Both research projects are representative of the research performed at the Department of Medicinal Chemistry, University Centre for Pharmacy, Groningen, presently led by Prof. Dr. H.V. Wikström. The second research project is performed in collaboration with the Department of Pharmacology (Prof. Dr. M.L. Dubocovich), Northwestern University Medical School, Chicago (USA), and Glaxo Group Research Ltd., Ware (UK).

SCOPE OF THE THESIS

Based on the hypothesis developed in the 1980's that stimulation of both dopamine D₁ and D₂ receptors would be needed for a good clinical result in the early stages of Parkinson's disease, the aim of the first part of this thesis was to develop a novel 2-aminotetralin as a mixed D₁/D₂-receptor agonist. Ultimately, such an agent could be used clinically in conditions where stimulation of D₁ receptors as well as D₂ receptors is needed. Chapters 1 to 3 constitute this part of the thesis. Chapter 1 provides a general introduction on central dopamine neurotransmission, dopamine receptors, dopamine-receptor agents, and dopamine-receptor interactions. Chapters 2 and 3 describe the synthesis and the pharmacological evaluation of 5,6-dihydroxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]tetralin [5,6-(OH)₂-PTAT] as a mixed D₁/D₂-receptor agonist. In addition, these chapters describe the development of 5,6-methylenedioxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]tetralin [5,6-OCH₂O-PTAT] as a potential prodrug of 5,6-(OH)₂-PTAT.

Based on the successful development of 2-aminotetralins as serotonin-receptor agents, and taking into account the similarities and differences between the chemical structures of the neurotransmitter serotonin and the hormone melatonin, the aim of the second part of this thesis was to develop 2-amidotetralins as nonindolic melatonin-receptor agents. These agents could play an important role in the characterization of melatonin receptors as well as in the elucidation of the mode of action of melatonin. Chapters 4 to 6 make up this part of the thesis. Chapter 4 merely reviews the current status of melatonin research. Chapter 5 deals with the synthesis and pharmacological evaluation of 8-methoxy-2-amidotetralins and related compounds as melatonin-receptor agonists. Chapter 6 describes the synthesis and pharmacological evaluation of 4-benzyl- and 4-phenyl-2-amidotetralins as melatonin-receptor agonists and antagonists, respectively.

In the general discussion the use of the 2-aminotetralin system as a structural base for the development of conformationally restricted analogues of different kinds of biologically active substances, such as dopamine and melatonin, is evaluated.